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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Dennis M. Klinman

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EXAMINER

ARCHIE, NINA

ART UNIT

PAPER NUMBER

1645

NOTIFICATION DATE

DELIVERY MODE

01/24/2011

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/682,130	Applicant(s) KLINMAN ET AL.	
	Examiner NINA A. ARCHIE	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35,46,47,54-61,65-74,76-78,80-89 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 54 and 60 is/are allowed.
- 6) ☒ Claim(s) 35,46,47,61,65-74,76-78,80 and 84-89 is/are rejected.
- 7) ☒ Claim(s) 62-64 and 81-83 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☐ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8, 2010 has been entered.
2. The declaration under 37 CFR 1.132 filed 12/8/2010 by Dennis Klinman dated 12/6/2010 is considered.

Amendment Entry

3. The amendment filed December 8, 2010 has been entered. Claims 46 and 54 have been amended. Claims 1-34, 36-45, 48-53, 55-59, 75, and 79 are cancelled. Claims 88-89 new. Claims 35, 46, 47, 54, 60-74, 76-78 and 80-89 are pending in the instant application.

Withdrawal of Objection/Rejection

4. The rejection of claims 54, 60, 62-64, and 81-83, under 35 U.S.C. 112, first paragraph (scope of enablement) has been withdrawn in view of applicant's arguments and Applicants Declaration on 12/8/2010.
5. The objection of the disclosure because of the specification and declaration reciting "RAW 246.7 cells" (see pg. 2 of declaration and example 2 of the specification) and the specification reciting "RAW 264.7 cells" (see example) has been withdrawn in view of applicant's arguments and the amendment to the specification on 12/8/2010.

Response to Arguments

6. Applicant's arguments with respect to claims 35, 46-47, 61, 65-74, and 76-78, 80, and 84-87 have been considered but are moot in view of the rejections in the previous office action.

Claim Rejections Maintained-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 35, 46-47, 61, 65-74, and 76-78, 80, and 84-89 are rejected under 35 U.S.C. 112, first paragraph (scope of enablement) for the reasons set forth in the previous Office Action in the rejection of claims 35, 46-47, 61, 65-74, and 76-78, 80, and 84-87.

The specification is enabled for a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

Additionally the specification is enabled for a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

However the specification does not reasonably provide enablement for a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2,

interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (claim 35). Moreover, the specification does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph (scope of enablement), December 8, 2010 are carefully considered, but not found to be persuasive for the reasons below.

Applicant arguments:

(A) Applicants argue that the amended claims are limited to reducing ODNs and have a specified sequence, length, and physical characteristics.

(B) Applicants argue the state of the prior art. Applicants argue the synthesis of ODNs, administration of ODNs to a subject of interest, and art- recognized models for testing therapies are well known in the art. Applicants argue the methods for measuring TNF, MIP-2, IL-6, and KC is well known in the art; kits to measure these cytokines are commercially available.

(C) Applicants argue the level of predictability in the art. Applicants argue the production of ODNs comprising the sequences set a specified nucleic acid sequence and of a specified length is routine in the art. Applicants argue there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. Applicants argue the Office has acknowledged that there are art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest in vivo. Applicants argue

exemplary results documenting the reduction in cytokine expression are also provided in the specification (see, for example, pages 34-35).

(D) Applicants argue the specification provides the sequences of the ODNs for use in the claimed methods (for example, Table 1, page 22). Applicants argue the specification further provides pharmaceutical compositions and methods of administration of ODNs (for example, page 24, line 9 to page 30, line 10) and methods for determining the effectiveness of an ODN, including methods for measuring cytokine or chemokine production (for example, page 30, line 11 to page 31, line 26; page 32, line 25 to page 34, line 16). Applicants argue the specification provides working examples wherein the claimed ODN reduce the production of TNF, MIP-2, IL-6, and KC in vitro (RAW 246.7 cells) and in vivo (a mouse model of lung inflammation) wherein the inflammation is induced by immunostimulatory CpG ODN. Applicants argue the specification provides the sequences of ODNs for use in the claimed methods and provides the use of an exemplary ODN (SEQ ID NO: 1) in inhibiting cytokine production in vitro (Example 2) and in an animal model of inflammation (Example 3).

(E) Applicants argue the Office action does not provide a single scientific reference or example from the specification to support the assertion that the results presented in the specification or the Declaration of Dr. Gursel cannot be extrapolated to inflammation induced by means other than immunostimulatory CpG ODN. Applicants argue the Office action has not provided "a reasonable basis to question enablement" (see MPEP § 2164.04).

(F) Applicants argue the Klinman Declaration discloses that immunostimulatory CpG ODN mimic the immunostimulatory activity of bacterial DNA, and provides a scientific references (Exhibits A and B) that disclose that immunostimulatory CpG motifs act through Toll like receptor 9 (TLR9) and/or TLR7 to directly stimulate human B cells and plasmacytoid dendritic cells, promote the production of Th 1 and proinflammatory cytokines, and trigger maturation of antigen presenting cells. Thus, immunostimulatory CpG ODN merely serve as a model agent that activates TLR9 and/or TLR7 and produce an inflammatory cascade. An anti-inflammatory agent that suppresses cytokine secretion induced by the biological pathway activated by these TLR receptors would suppress cytokine secretion. The means used to activate the TLR receptor would not alter the effect of the anti-inflammatory agent on the biological pathway. Thus, whether cytokine secretion was induced by immunostimulatory CpG ODN,

bacterial DNA, or another means, oligodeoxynucleotide of 10 to 30 nucleotides in length that comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21 would have the same effect on cytokine/chemokine production. As disclosed in the Klinman Declaration, the biological action of a suppressive ODN does not result from the agent used to induce inflammation, but results from the biological mechanisms triggered through the TLR receptor.

Specifically, the Klinman Declaration (and accompanying Exhibit A) also provides evidence that a suppressive ODN A151 (SEQ ID NO: 2) suppresses inflammation induced by collagen and lipopolysaccharide. Furthermore, the Klinman Declaration (and accompanying Exhibit C) provides evidence that H154 (SEQ ID NO: 1, presently claimed) reduces the production of TNF α , MIP-2, IL-6 and KC induced by bacterial DNA. Thus, the Klinman Declaration provides evidence that the methods described in the specification are fully enabled, regardless of whether the agent that induces the inflammation is a CpG ODN, bacterial DNA, or another means.

Thus, the Klinman Declaration provides direct evidence that, one of skill in the art, using the general methods described in the specification, could use the ODNs comprising SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21 to reduce the production of TNF α , MIP-2, IL-6 and KC. Applicants submit that the specification is fully enabling for reducing the production of TNF α , MIP-2, IL-6 and KC induced by a variety of inducing agents.

Examiner's Response to Applicant's Arguments:

With regard to Point (A), the specification discloses a (ODN) H154 (SEQ ID NO: 1) as a suppressive oligodeoxynucleotide and CpG ODN 1555 (SEQ ID NO: 27) as the immunostimulatory oligonucleotide, and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33)). The specification discloses the administration of inhaled isoflurane, and ODNs to mice whereby the mice were sacrificed to determine cytokine concentrations (see Example 1). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNF α , MIP-2, IL-6, and keratinocyte-derived cytokine [KC]) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated

RAW 246.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production of cytokines and chemokines (TNF α , MIP-2, IL-6, and KC), wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNF α and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4). Therefore the specification is limited to a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject with lung inflammation and b) administering to the subject diagnosed with lung inflammation, a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. The examples and data set forth in the specification do not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with any subject population. The specification is directed to a specific subject population. Therefore the specification is not representative of the instant claims. Therefore although the claims have been amended and narrow in scope, the specification is not representative of the claims.

With regard to Point (B), Examiner agrees the synthesis of ODNs, administration of ODNs to a subject of interest is used in art-recognized models for testing therapies are well known in the art. Examiner agrees with the methods for measuring TNF, MIP-2, IL-6, and KC are well known in the art and kits to measure these cytokines are commercially available. Examiner agrees the level of ordinary skill in the art is of a molecular biologist and/or pulmonologist is high. Examiner agrees that with the disclosed ODN sequences that one of skill in the art could readily make and use the claimed invention; however the specification is not representative of the instant claims. Consequently, the examples and data set forth in the

specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with a subject population diagnosed with inflammatory lung disease.

With regards to Points (C), (D), and (E), Examiner agrees the art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest in vivo however the claims are not limited to the instant invention. Examiner agrees the production of ODNs comprising the sequences set a specified nucleic acid sequence and of a specified length is routine in the art. Examiner agrees there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. However, the claims are drawn to a method of reducing the production of TNF α , MIP-2, IL-6, and KC comprising administering a suppressive oligodeoxynucleotide of SEQ ID NOs: 1, 14, 17, 18, 19 and 21 or a combination thereof and a method of reducing the production TNF α , MIP-2, IL-6, and KC in a cell in vitro, comprising contacting the cell with suppressive oligodeoxynucleotide of SEQ ID NOs: 1, 14, 17, 18, 19 and 21 or a combination thereof. Moreover the specification discloses a (ODN) H154 (SEQ ID NO: 1) as a suppressive oligodeoxynucleotide and CpG ODN 1555 (SEQ ID NO: 27) as the immunostimulatory oligonucleotide, and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33)). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNF α , MIP-2, IL-6, and keratinocyte-derived cytokine [KC]) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated RAW 246.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production of TNF α , MIP-2, IL-6, and KC, wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNF α and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4)). Consequently, the specification is limited to a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject with lung inflammation and b) administering to the

subject with lung inflammation, a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. Hence one skilled in the art would accept the in vivo efficacy to correlate to the in vitro data. However, there is no indication from the instant claims that the cytokine or chemokine production has been increased or is increased which would require a need to reduce it.

Moreover the declaration discloses results documenting the reduction in cytokine expression of TNF α , MIP which is not directed to MIP-2, IL-6, and KC in vitro by contacting a cell with an immuostimulatory CpG and a suppressive oligodeoxynucleotide selected from the group consisting of SEQ ID NOs: 14, 17, 18, 19 and 21 (see pgs. 2-3 of declaration filed 6/18/2010 and 12/8/2010). Therefore the declaration is limited to a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. Therefore the declaration is also limited to a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is one or more SEQ ID NOs: 14, 17, 18, 19 and 21 because one skilled in the art would accept the in vitro data to correlate with in vivo efficacy. Consequently, the declaration under 37 CFR 1.132 filed 6/18/2010 signed by Ihsan Gursel, Ph.D. and 12/8/2010 signed by Dennis Klinman are insufficient to overcome the rejection because the evidence in the declaration is not commensurate in scope with the instant claims which are not limited to a specific subject population (i.e. subject with lung inflammation), thus the Declaration is deemed unpersuasive. Even though the declaration provides a scientific explanation and citations that support the assertion that one of skill in the art would also accept that the production of these

cytokines should also be reduced, the declaration is unpersuasive because the evidence in the declaration is not commensurate in scope with the instant claims. The declaration is enabling for the specification but the declaration does not enable for the instant claims. Consequently, the examples and data set forth in the declaration and in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with any subject population.

As outlined previously, the specification is enabled for a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

Additionally the specification is enabled for a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

However the specification does not reasonably provide enablement for a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide

comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (claim 35).

Moreover, the specification does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The claims are drawn to a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid

sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (claim 35); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC) in a cell in vitro, comprising contacting the cell specifically with a suppressive oligodeoxynucleotide, wherein the suppressive oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 54).

Breadth of the claims: The claims encompasses suppressive oligodeoxynucleotides (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more suppressive oligodeoxynucleotides thereof (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) in a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering solely one or more suppressive oligonucleotide in vivo or in vitro without the administration of an immunostimulatory CpG with one or more said suppressive oligodeoxynucleotides is overly broad. Therefore it is hard for one skilled in the art to determine if the suppressive oligodeoxynucleotides (SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more can be used for in the recited methods as claimed. Furthermore it is hard for one skilled in the art to determine if the performance of the recited methods correlate to the outcome of a method of reducing the production of a (TNF), (MIP)-2, (IL)-6 or (KC) in any subject population. The invention is directed to specific subject population and there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with any non-specific subject population.

Guidance of the specification/The existence of working examples:

The specification discloses a suppressive oligodeoxynucleotide (ODN) H154 (SEQ ID NO: 1), CpG ODN 1555 (SEQ ID NO: 27), and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNF α , MIP-2, IL-6, and KC) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated RAW 264.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production (TNF α , MIP-2, IL-6, and KC), wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNF α and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4).

Consequently, the specification is limited to a method of reducing the production of TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. Hence one skilled in the art would accept the in vivo efficacy to correlate to the in vitro data. However, the examples and data set forth in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo or in vitro with no specific subject population. Therefore the specification is not representative of the instant claims and the specification is not fully enabled for the instant claims.

In conclusion, the claimed invention does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering

Art Unit: 1645

specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46). The claims encompass the suppressive oligodeoxynucleotides (SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more suppressive oligodeoxynucleotides thereof (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) in a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only one or more suppressive oligonucleotide in vivo solely without the administration of an immunostimulatory CpG with one or more said suppressive oligodeoxynucleotides with no specific subject population is overly broad. Therefore it is hard for one skilled in the art to determine if the performance of the recited methods correlate to the outcome of a method of reducing the production of a (TNF), (MIP)-2, (IL)-6 or (KC) in a subject with a non-specific subject population in vivo because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with no specific subject population. The specification is limited to a method of reducing the production TNF α , MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell in vitro, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NOs: 1, 14, 17-18, 19, and 21. However, the examples and data set forth in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNF α , MIP-2, IL-6, and KC administering only a suppressive oligonucleotide in vivo with a non-specific subject population. Therefore the specification is not representative of the instant claims and the specification is not fully enabled for the instant claims. Moreover, since the specification and declaration filed on 12/8/2010 is not representative of the instant claims, the claimed methods are not enabled.

Objection

6. Claim 74 is objected under 37 CFR 1.75 as being a substantial duplicate of claim 70. When two claims in an application are duplicates or else are so close in content that they both

Art Unit: 1645

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

7. Claim 54 and 60 are allowed.

Claims 62-64 and 81-83 are objected to as being dependent from a rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Patricia Duffy can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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REM 3B31

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